IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
David FIKSTAD et al.	Group Art Unit: 1618
Application No.: 09/871,318	Examiner: Micah Paul Young
Filed: May 31, 2001	Confirmation No.: 1207
For: TRANSDERMAL DELIVERY OF LASOFOXIFENE	

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is from the Advisory Action mailed March 4, 2009, finally rejecting many of the pending claims in the above-cited application. A Notice of Appeal was timely filed on March 12, 2009.

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I. REAL PARTY IN INTEREST

The Real Party in Interest in the instant application is Watson Pharmaceuticals, Inc., the assignee of record. Pfizer, Inc. is also a Real Party in Interest as the sole licensee of the instant application.

II. RELATED APPEALS AND INTERFERENCES

An Appeal in the instant Application was decided on August 27, 2008 under Appeal No. 2008-3445. There are no other prior or pending Appeals, Judicial Proceedings or Interferences known to the Appellant which may be related to, directly affect or be directly affected by or have bearing on the Board's decision in the instant Appeal.

III. STATUS OF CLAIMS

Claims 1, 2, 6-13, 15-16 and 20-21 have been canceled.

Claims 14, 18, 19 and 25-27 stand rejected and are appealed.

Claims 3-5, 17, 22-24 and 28-40 have not been canceled or withdrawn in light of the Board's rejection dated August 27, 2008 should further appeals be in order.

IV. STATUS OF AMENDMENTS

There have been no amendments filed subsequent to the December 12, 2008 final rejection.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 14 pertains to a device for administering an active agent to the skin or mucosa of an individual comprising a laminated composite of:

- a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk (*See* application page 10, lines 26-28);
- an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer (*See* application page 10, lines 28-30);
- the backing layer and membrane defining a reservoir therebetween that contains a transdermal formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof (*See* application page 10, lines 30-31);
- the peel seal disc underlying an active agent-permeable membrane (*See* application page 10, line 31);
- a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer (*See* application page 10, lines 31-33);
- an adhesive overlay having a central portion overlying the backing layer and a peripheral portion that extends beyond the periphery of the peel seal disc (*See* application page 10, line 35); and
- a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc (*See* application page 11, lines 2-3).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 14, 18, 19 and 25-27 are obvious under 35 U.S.C. § 103 in view of Ebert *et al.* (U.S. Patent No. 5,662,925), Cormier *et al.* (U.S. Patent No. 6,203,817) in view of Ke *et al.* (U.S. Patent No. 6,323,232).

VII. ARGUMENT

A. The Pending Claims are Appealed in Light of New Evidence Presented

On August 27, 2008 within Appeal No. 2008-3445, the Board maintained the Examiner's rejections of many of the pending claims. Those claims where the Examiner's rejections were not upheld were rejected by the Board *sua sponte*. In response to these rejections, Appellants submitted the declaration of Dr. Andrew Coop under 37 C.F.R. § 1.132 after the application returned to *ex parte* prosecution (See Exhibit A). The declaration provides evidence in support of Appellants' arguments that the pending claims are not obvious in view of the publications asserted by the Examiner.

Since the Board's earlier decision was rendered without consideration of the Coop Declaration, Appellants maintain that this evidence and the arguments presented herein demonstrate that one of ordinary skill in the art would not find the combination of publications cited by the Examiner to render the claimed invention to be obvious. The Appellants consider the Examiner to have oversimplified the complexities involved in formulating a transdermal drug delivery system and to have mischaracterized the cited publications. Dr. Coop's declaration is discussed in detail below.

B. The Legal Standard

To establish a *prima facie* case of obviousness, several tenets of patent law must be adhered to. For example, "under [35 U.S.C.] § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness

or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unresolved need, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *KSR,* 550 U.S. 398, 406; 82 U.S.P.Q.2d 1385, 1391 (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). It "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine . . . elements in the way the claimed new invention does. This is so because invention in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 550 U.S. 398, 418-419; 82 U.S.P.Q.2d 1385, 1396. In addition, fact finders "should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 550 U.S. 398, 421; 82 U.S.P.Q.2d 1385, 1397 (citing *Graham's* warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight").

The focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge." 72(195) Fed. Reg. 57526, at 57527 (Oct. 10, 2007).

Here, the Examiner has foregone the requirements of *KSR* and asserted that the claimed invention is obvious by mischaracterizing the publications cited and failing to take into account basic principles of pharmacology, chemistry and pharmaceutics known to those of ordinary skill in the art. When viewed objectively, with consideration of the Graham factors and without the

benefit of hindsight reasoning, Appellants submit that Claims 14, 18, 19 and 25-27 do not violate 35 U.S.C. § 103(a), *i.e.*, Claims 14, 18, 19 and 25-27 are not obvious over the cited publications.

C. The Rejection of Claims 14, 18, 19 and 25-27 Under 35 U.S.C. § 103(a)

Claims 14, 18, 19 and 25-27 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious in view of Ebert (U.S. Pat. No 5,662,925), Cormier (U.S. Pat. No. 6,203,817) and Ke (U.S. Pat. No. 6,323,232).

The Examiner has stated that the basis for the rejection is as follows:

> The '925 patent discloses a transdermal delivery device comprising an [sic] backing layer, an active agent, a reservoir, a peel seal disc, a heat seal, an adhesive overlay and a removable release liner (Figure 1, col. 2, lin. 60 to col. 3, lin. 10). The reference is however silent to the inclusion of lasofoxifene. It would have been well within the level of skill in the art to include a transdermal lasofoxifene formulation into the device as shown in the '817 and '232 patent. (*See* Final Action at page 3).

The Examiner then stated, in-part, that:

> The '817 patent discloses a transdermal formulation comprising an adhesive matrix reservoir (abstract). The transdermal attached to the skin and comprises an adhesive overlay (part 22), a backing layer attached to the overlay (part 14), a reservoir under said backing layer (part 12), an optional active agent -permeable layer under said reservoir, a further disc layer (part 24), and a release liner (not pictured) (column 9, line 21-60). The device is further sealed to prevent leakage (column 9, line [sic] 30-35). The transdermal device further comprises permeation enhancers such as ethanol or propylene glycol (column 10, lines 5-29; examples). The transdermal comprises a gel matrix comprising gelling agents such as hydroxypropylcellulose and colloidal silicone dioxide (column 10, lines 22-39). The transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene (column 7, lines 66-68; column 8, lines 9-12). (*See* Final Action at page 3).

Finally, the Examiner stated, in-part, that:

> The '232 patent discloses a combination of active agents in a transdermal comprising including [sic] lasofoxifene and other estrogen agonists/antagonists

> (claim 1). Among other agents used in the combination therapy are droloxifene, raloxifene and tamoxifen (column 6, lines 35-40)...These agents are identical to those preferred in the '817 patent and act as functional equivalents of each other. (*See* Final Action at pages 3-4).

These assertions, however, are based on a mischaracterization of the cited '232 patent because it does not describe lasofoxifene in a relevant transdermal form. In particular, the '232 disclosure is directed to a divergent formulation that would not suggest the claimed transdermal formulation. Moreover, the Examiner's arguments are based on the false presumption that compounds with similar pharmacological activities necessarily have similar chemical properties. However, there is no basis in law or science for a particular drug in a pharmacological class to render obvious other chemically unrelated drugs in that class. This is particularly true because the chemical properties of drugs are the determining factors that dictate which drugs may be incorporated into a formulation.

Still further, the Examiner did not afford the proper weight to the declaration filed under 37 C.F.R. § 1.132 in support of the patentability of the claims. Also, the Examiner's response addressed claims that are not currently pending and did not properly respond to the points raised by the Declarant.

1. The '232 Patent Does Not Disclose a Transdermal Form of Lasofoxifene That Would be Obvious to Use in the Claims under Appeal.

The Examiner acknowledges that neither the '952 patent nor the '817 patent discloses lasofoxifene (*see* Final Office Action dated 12/12/08, page 3, last sentence of the second paragraph). The Examiner attempted to make up for this shortfall by asserting that the '232 patent disclosed "a transdermal" form of lasofoxifene that would be obvious to combine with the

disclosures in the '925 and '817 patents. (*See* '232 patent claims 1 and 2 at col. 40, lines 48-55). This assertion, however, is flawed because it mischaracterizes the formulation disclosed in the '232 patent.

Unlike the transdermal drug delivery device claimed in the instant application, the '232 patent only discloses a liquid solution for topical administration. For example, at col. 37, lines 49-52 the specification states that:

> For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

This type of solution is markedly different from the transdermal drug delivery system claimed in the instant application. For instance, the presently claimed system permits uninterrupted therapy and reversibility of treatment (*see* US 2002/0037311, para. [0007]), both of which are not possible using a parenteral solution poured on the skin as disclosed in the '232 patent.

In order to provide both uninterrupted therapy and reversibility of treatment, the drug must interact appropriately with the polymer layer, the enhancer, the drug reservoir, the matrix, and any other compounds or adjuvants in the formulation. This principle is confirmed by the Declaration of Dr. Coop, a pharmaceutical scientist who has significant experience in the field and would be considered to be one of ordinary skill in the art (*See* Exhibit A). In his Declaration, Dr. Coop testifies that the ability for the drug to interact appropriately with all of these variables would not be known to one of ordinary skill in the art from the disclosure of an aqueous solution. (*See* Exhibit A - "Coop Declaration" at para. 13). Dr. Coop also testifies that the chemical characteristics of a drug drive how it interacts with its environment. These chemical

characteristics, in turn, are defined by the structural make-up and functional groups possessed by a drug. (*See* Exhibit A - "Coop Declaration" at paras. 8-11). The very fact that these functional groups differ is the sound reasoning demonstrating why chemical structure affects properties such as the stability of the active ingredient, the stability of the adjuvant in combination with the active ingredient, the phase distribution of the compound within a matrix, the release of the compound from the matrix, pH and bioavailability. These differing physical and chemical properties, however, were not accounted for by the Examiner in formulating the obviousness rejection.

As Dr. Coop testifies, the fact that several assumptions must be made based on unpredictable components would not lead one of ordinary skill in the art to conclude that lasofoxifene in an aqueous solution could be successfully and predictably used in a transdermal drug delivery system. (*See* Exhibit A - "Coop Declaration" at para. 13).

Thus, one of ordinary skill in the art would not reasonably conclude that the parenteral solution of the '232 patent could be incorporated into the claimed transdermal drug delivery system. Accordingly, the Examiner has not demonstrated that the claimed invention is *prima facie* obvious in view of the cited publications.

2. Individual Drugs From a Pharmacological Class Do Not Render the Use of Another Drug From the Same Class Obvious When They are Chemically Unrelated.

It is a well-established principle of patent law that compounds of similar *structure* are presumed to have similar properties. *See, In re Dillon*, 919 F.2d 688, 692-693; 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990). However, there is *no* legal basis for presuming the converse, *i.e.*,

that compounds with similar pharmacological activities necessarily have similar chemical properties or characteristics. In fact, the opposite is true. It is well-established that "the mere inclusion of several compounds in a list of compounds...does not necessarily establish that each of those compounds is equivalent to the others for all purposes." *See, e.g., In re Jezl*, 396 F.2d 1009, 1012; 158 U.S.P.Q. 98, 99-100 (CCPA 1968). The Federal Circuit has also stated that when a chemical compound has an insufficiently similar structure, other chemical compounds in the same genus are not prima facie obvious. *See, e.g., In re Jones* 958 F.2d 347, 350; 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992). In the present case, however, the Examiner has disregarded this well-established law. Instead, the Examiner argues that where compounds have similar pharmacologic activity, that activity is sufficient to render obvious the use of every compound in a formulation merely because of their shared therapeutic effect, *without regard for whether the compounds share any structural similarity.*

It is well known in the art that a compound's pharmacological classification is based on the behavior a compound exhibits in the human body and not on its chemical make-up. For example, antiestrogenic compounds have a single characteristic in common - they work against the effect of estrogen *in vivo*. It is only because of this activity that they are listed together under the pharmacologic class of antiestrogenic compounds. The Examiner's assertion, however, that the use of lasofoxifene in the claimed device would be obvious because it is an antiestrogenic agent and "a functional equivalent" of the other compounds listed is not supported by law. It is well-established that "[e]xpedients which are functionally equivalent to each other are not necessarily obvious in view of one another." *See, e.g., In re Scott*, 323 F.2d 1016, 1019; 139 U.S.P.Q. 297, 299 (CCPA 1963). And, in this case, the difference in chemical makeup of the

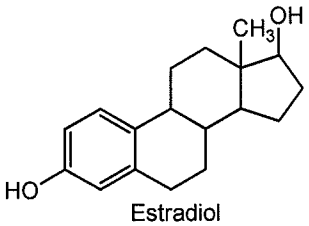
compounds despite their common pharmacologic classification demonstrates that they are not obvious in view of one another.

In addition, the Examiner's assertion of obviousness is based on an analysis that skips a step required by law, and by the MPEP. For claims that involve chemical compounds, a proper obviousness analysis first requires the Examiner to consider similarities in chemical structure. MPEP 2144.08 II.A.4.(d) states that the Examiner should "[c]onsider the properties and utilities of the *structurally similar* prior art species or subgeneus." Thus, only after compounds are found to have structural similarity are the properties of those compounds considered.

As discussed above and emphasized here, the Examiner's own statements demonstrate that he has not taken into account the differences between the compounds asserted to be "functional equivalents." For example, the Examiner stated in the first full paragraph on page 4 of the Office Action dated December 12, 2008 that:

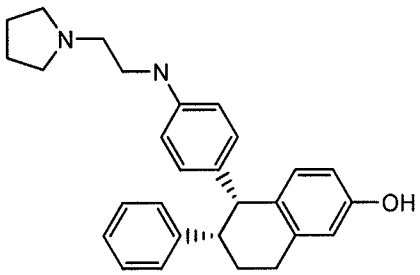
> It would have been obvious to a person of ordinary skill in the art to combine the device of the '925 patent with the transdermal administration of lasofoxifene shown in the '817 patent and the '232 patents since Ebert discloses that the device is useful for the administration of a variety of agents in **including estradiols** (col. 4, lin. [sic] 20). [emphasis added]

The Examiner's inclusion of lasofoxifene with a discussion of estradiols demonstrates that he has failed to account for the differences in chemical properties between lasofoxifene and these other compounds and has strictly focused on the common pharmacologic class. As discussed above, the analysis should first focus on a comparison of the structural similarities of the compounds rather than their pharmacologic nature. *See* MPEP 2144.08 II.A.4.(d). For example, estradiols possess the following chemical structure that, in turn, has unique chemical properties:



Estradiol [1]

The reference to estradiols in the '925 patent does not refer to or suggest compounds such as lasofoxifene having the following very different structure:



Lasofoxifene

Appellants have submitted a declaration under 37 C.F.R. § 1.132 of an expert outlining the differences in structure among the compounds in the publications cited and how these differences must be taken into account when formulating transdermal delivery devices since they introduce unpredictability. (*See* Exhibit A "Coop Declaration" at para. 11). In fact, there is no evidence that the Examiner considered Dr. Coop's testimony regarding this unpredictability (*See* Discussion in § VII.C.3 below).

In his Declaration, Dr. Coop testifies that the chemical makeup and functional groups possessed by the compounds described in Cormier are significantly different from those of lasofoxifene even though they possess a common pharmacological classification. The fact that two compounds are members of the same pharmacologic class only indicates that they are

[1] See Hawley's Condensed Chemical Dictionary (Eleventh Edition) 1987.

expected to have similar therapeutic effect on the body. The knowledge of a formulation using one drug from a pharmacologic class would not suggest the use of other drugs in the same class without evidence of similarity in chemical and physical properties for purposes of formulation.

In view of this, the Examiner has not provided the reasoning necessary to prompt one of ordinary skill in the art to combine the publications cited. Instead, it appears that the Examiner has simply employed impermissible hindsight reasoning, using the claims as a template to search the U.S. Patent database in order to find all of the elements of the instant claims. Such reasoning is legally impermissible. Accordingly, it is respectfully requested that this rejection be withdrawn.

3. The Examiner Failed to Afford Proper Weight to the Declaration Submitted Under 37 C.F.R. § 1.132.

In the Final action dated December 12, 2008, the Examiner stated that the affidavit submitted under 37 C.F.R. § 1.132 was insufficient to overcome the rejection of claims 14, 18, 19 and 25-27 under 35 U.S.C. § 103(a). In making this assertion, the Examiner stated that:

> [T]he Declaration is an opinion Affidavit by an unrelated party. The opinion affidavit argues that [*sic*] same points put forth in previous responses to prior art rejection. Lasofoxifene is a different chemical structure than that of the other listed compounds in the Ke and Cormier patents. However, as stated in the Board Decision dated 8/27/08 the Ke patent provides transdermal formulation for lasofoxifene (claim 1), raloxifene or tamoxifen (claims, col. 3, lin. 49). Cormier provides transdermal formulation for tamoxifen and raloxifene, establishing that though difficult, the artisan of ordinary skill is able to include differing active compounds within a similar carrier formulation despite differences in chemical structure. Their functions and intents remain the same and as such it remains obvious.

The Examiner, however, did not address each of the points raised in the Coop Declaration. Rather, the Examiner only reiterated an assertion raised by the Board in the prior

appeal in this case, relating to different claims than those at issue. What is more, the Board's decision in the prior appeal was rendered without consideration of the Coop Declaration, which was filed after the application returned to *ex parte* prosecution.

"When an applicant timely submits evidence traversing a rejection, the examiner must reconsider the patentability of the claimed invention." MPEP 716.01(d). The Examiner's response, however, does not demonstrate that the patentability of the claimed invention was ever reconsidered. By restating the position of the Board with regard to claim 1, it appears that the patentability of a differing claim and not the pending claims was the only consideration made (*See* Final Office Action Dated December 12, 2008 at page 3). Since the Examiner did not address independent claim 14 and those claims that depend therefrom, he did not fulfill the requirements under MPEP 716.01(d).

"Where the evidence is insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient." MPEP 716.01(b). As discussed above, the Examiner only reiterated the Board's position with regard to claim 1 and did not address the point raised in the Coop Declaration. Such a reiteration does not address the sufficiency of the evidence submitted by Appellants. As a result, the Examiner also did not fulfill his duties under MPEP 716.01(b).

In light of the Examiner's failure to properly consider the evidence of non-obviousness submitted in the declaration under 37 C.F.R. § 1.132, it is respectfully requested that the Board assign the proper weight to this evidence and find the pending claims to be non-obvious.

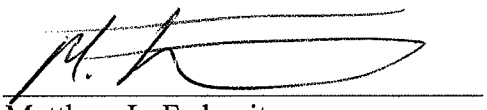
VIII. CONCLUSION

In view of the foregoing arguments, Appellant respectfully request reconsideration and withdrawal of the claim rejections, and that the application be passed to issuance. Failing that, Appellants respectfully request the Board to overrule the Examiner's rejections, based on the explanations presented above, and to pass this application to issuance.

Only an Appeal Brief fee is believed to be due at this time. Should any additional fee be required, please charge such fee to Bingham McCutchen, LLP Deposit Account No. 50-4047.

Respectfully submitted,

BINGHAM MCCUTCHEN, LLP

Date: May 12, 2009 By: 

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IX. CLAIMS APPENDIX

1.-2. (Canceled)

3. (Previously Presented) A transdermal formulation comprising an adhesive drug matrix reservoir and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

4. (Previously Presented) The transdermal formulation of claim 3, wherein the adhesive matrix is a solvent based pressure sensitive adhesive matrix.

5. (Previously Presented) The transdermal formulation of claim 3, wherein the adhesive matrix is a water based pressure sensitive adhesive matrix.

6.-13. (Canceled)

14. (Previously Presented) A device for administering an active agent to the skin or mucosa of an individual comprising a laminated composite of:

a. a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk;

b. an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer, the backing layer and membrane defining;

c. the reservoir therebetween that contains a transdermal formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof;

d. the peel seal disc underlying an active agent-permeable membrane;

e. a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer;

f. an adhesive overlay having a central portion overlying the backing layer and a peripheral portion that extends beyond the periphery of the peel seal disc; and

g. a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc.

15.-16. (Canceled)

17. (Previously Presented) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of any of claims 3 to 5.

18. (Previously Presented) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with the device of claim 14.

19. (Previously Presented) A method for treating or preventing a disorder associated with estrogen deficiency in a subject comprising contacting a dermal situs of the subject with the device of claim 14.

20.- 21. (Canceled)

22. (Previously Presented) The method of claim 17, wherein the pharmaceutical formulation further comprises a drug permeation enhancer.

23. (Previously Presented) The method of claim 22, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

24. (Previously Presented) The method of claim 23, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

25. (Previously Presented) The device of 14, wherein the pharmaceutical formulation further comprises a drug permeation enhancer.

26. (Previously Presented) The device of claim 25, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

27. (Previously Presented) The device of claim 26, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

28. (Previously Presented) A transdermal device comprising a means for adhering a drug reservoir to the application situs and the transdermal formulation of any of claims 3 to 5.

29. (Previously Presented) The transdermal device of claim 28, wherein the transdermal formulation further comprises an effective amount of a drug permeation enhancer.

30. (Previously Presented) The device of claim 29, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

31. (Previously Presented) The device of claim 30, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

32. (Previously Presented) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a free form hydroalcoholic gel and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

33. (Previously Presented) The method of claim 32, further comprising an effective amount of a drug permeation enhancer.

34. (Previously Presented) The method of claim 33, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

35. (Previously Presented) The method of claim 34, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

36. (Previously Presented) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a liquid reservoir drug formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

37. (Previously Presented) The method of claim 36, further comprising an effective amount of a drug permeation enhancer.

38. (Previously Presented) The method of claim 37, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

39. (Previously Presented) The method of claim 38, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

40. (Previously Presented) The transdermal formulation of claim 3, 4, or 5, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

X. EVIDENCE APPENDIX

Exhibit A - Declaration under 37 C.F.R. 1.132 by Dr. Andrew Coop entered into the record on October 27, 2008.

XI. RELATED PROCEEDINGS APPENDIX

Exhibit B - Decision in Appeal No. 2008-3445.

EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
David FIKSTAD et al.	Group Art Unit: 1618
Application No.: 09/871,318	Examiner: Micah Paul Young
Filed: May 31, 2001	Confirmation No.: 1207
For: TRANSDERMAL DELIVERY OF LASOFOXIFENE	

DECLARATION UNDER 37 CFR.1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Andrew Coop, declare as follows:

1. I am a permanent resident of the United States, and reside at 9462 Ridgeview Drive, Columbia, MD 21046

2. I am currently a Professor and Chair of the Department of Pharmaceutical Sciences at the University of Maryland School of Pharmacy. I have been employed as Chair of the Department for 15 months, and oversee 23 faculty members with interests from molecular biology, to pharmacology, to chemistry, to pharmaceutics and drug delivery, to clinical sciences. I have been employed in the faculty position for ten years. In this position, I have overseen a medicinal chemistry program utilizing modern drug design techniques and novel organic methodology in the design and synthesis of ligands targeted at biological systems involved in drugs of abuse and cancer. The most relevant work to

this declaration includes my studies on opioids, Gamma-hydroxybutyrate, and sigma receptor antagonists. Prior to my current employment, I was a Fogarty Fellow in the Laboratory of Medicinal Chemistry at the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health. In this position, I focused my work on analogs of naltrindole, and new methodology.

3. I received my Bachelor's and Master's degrees from St. Catherine's College, at the University of Oxford. While obtaining these degrees, I performed research on organo-lean and tin compounds.

4. I received my Ph.D. in Chemistry from the School of Chemistry at the University of Bristol where I focused my research on ring constrained analogues of buprenorphine.

5. As part of this opinion, I would consider a person who is skilled in the field of the invention to be one having a doctoral degree in the fields of chemistry, pharmaceutics, pharmacology, medicinal chemistry or a related discipline.

6. I have reviewed the Fikstad et al. application (US 2002/0037311) and claims 14, 18, 19 and 25-27 and have been asked whether the combination of Ebert et al. (US 5,662,925), Cormier et al. (US 6,203,817) and Ke et al. (US 6,323,232) would result in these claims being obvious to a person who is skilled in the field.

7. My answer to this request, in short, is no, the combination of Ebert et al. (US 5,662,925), Cormier et al. (US 6,203,817) and Ke et al. (US 6,323,232) would not result in claims 14, 18, 19 and 25-27 being obvious to a person who is skilled in the field.

8. My opinion in this regard is based on the fact that the chemical properties of compounds listed in these publications ultimately dictate how they may be formulated. I also, believe that the combination of these publications relies on the false presumption that drugs may

be interchanged in different formulations based solely on their pharmacological classification.

9. To demonstrate why I believe that these compounds may not be interchange requires a comparison of lasofoxifene to tamoxifen, droloxifene, idoxifene, raloxifene HCl and tamoxifen citrate. In regard to the structure of lasofoxifene, I define this compound as possessing three aromatic rings that are constrained through a 6–membered restraining ring. As a result, the lasofoxifene structure is very different from all of the other drugs listed above which do not have a constraining ring, with the exception of Raloxifene that has a very different 5-membered sulfur-containing planar ring. The effect of these differences is that the constraint of these rings forces a different conformation to the non-constrained compounds, and will lead to significantly different physical properties compared to all other compounds listed. Each of these properties would, in turn, have an effect on the manner in which it is formulated.

10. In addition to the basic structure of the compounds differing, they all also possess differing functional groups from each other. For example, the compounds contain piperidine, pyrolidine, thiophene, phenol, carboxylic acid and halogenated aromatic groups. These functional groups affect properties such as the stability of the active ingredient, stability of the adjuvant in combination with the active ingredient, phase distribution within a matrix, release from the matrix, pH and bioavailability. All of which must be accounted for in formulating a transdermal formulation.

11. In sum, each of these differences in chemical make up of these compounds introduces a layer of unpredictability to the use of these compounds, especially with regard to formulations. And this unpredictability would then transcend to the unpredictability of

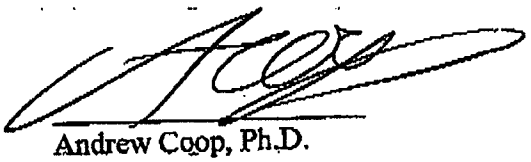
the kinetics by which a drug passes out of the matrix and into the patient receiving therapy.

12. In addition to the layers of unpredictability with regard to the chemical make-up of compounds, there is also unpredictability in the transdermal device in itself. For example, since each of the compounds listed in the Cormier, Ke and Ebert publication possess certain qualities with regard to solubility, pH etc., these would require modifications of the device that would require the differences in how each drug would interact with the other compounds or adjuvants in the formulation as well as the phase distribution in the matrix and the release form the matrix to be accounted for. As a result, the material make-up of the device would have to be varied to prevent degradation of the drug, increase stability of the drug, and provide bioavailability of the drug to the patient. All of which are unpredictable factors that may or may not lend a drug to being formulated for transdermal delivery.

13. In view of these unpredictable considerations in formulating a transdermal device for the delivery of lasofoxifene, I believe that one who is skilled in the field, would not recognize that the topical administration of an aqueous solution of lasofoxifene as described in Ke et al. would in any way predictably dictate that the same concept would translate to the transdermal delivery of lasofoxifene using the device and methods as set forth in claims 14, 18, 19, and 25-27. In fact, I believe that the topical administration of an aqueous solution of any drug would not be suggestive of whether that drug could be incorporated into a transdermal delivery device because many unpredictable factors must be taken into account not only with the drug, but also with the device itself as discussed above.

14. Therefore, it is my opinion that one who is skilled in the field would not find the transdermal device and methods for delivering lasofoxifene as set forth in claims 14, 18, 19 and 25-27 to be obvious in view of the combination of the Cormier, Ke and Ebert publications. This is because several assumptions must be made based on the unpredictable components would lead one who is skilled in the field to conclude that the combination of lasofoxifene in a transdermal drug delivery device and related methods of treatment would not be a predictable based on their established functions.

15. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code.



Andrew Coop, Ph.D.

October 27, 2008
Date

EXHIBIT B

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DAVID FIKSTAD and KANYI QUAN

Appeal 2008-3445
Application 09/871,318
Technology Center 1600

Decided: August 27, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods, pharmaceutical formulations, and devices for the transdermal delivery of lasofoxifene. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm in part and enter a new ground of rejection.

BACKGROUND

"Naturally occurring estrogens and synthetic compositions demonstrating 'estrogenic' activity are useful for various therapeutic applications" (Spec. 1). "Lasofoxifene (CP-336,156) is a selective estrogen receptor modulator (agonist/antagonist). It has been shown to have similar therapeutic effects in bone and LDL levels to estradiol but without the uterine-stimulating effects associated with estradiol therapy" (*id.* at 2).

"Transdermal delivery of drugs provides many advantages over conventional oral administration. Advantages of transdermal systems include convenience, uninterrupted therapy, improved patient compliance, reversibility of treatment (by removal of the system from the skin), elimination of 'hepatic first pass' effect, a high degree of control over blood concentration of the drug, and improved overall therapy" (*id.* at 3).

The Specification discloses "methods, pharmaceutical formulations, and devices for the transdermal delivery" of lasofoxifene (*id.*).

DISCUSSION

1. CLAIMS

Claims 3-5, 14, 17-19 and 22-40 are pending and on appeal. Claims 3, 14, 17, 30, 32 and 36 are representative and read as follows:

Claim 3: A transdermal formulation comprising an adhesive drug matrix reservoir and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

Claim 14: A device for administering an active agent to the skin or mucosa of an individual comprising a laminated composite of

a. a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk;

b. an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer, the backing layer and membrane defining;

c. the reservoir therebetween that contains a transdermal formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof;

d. the peel seal disc underlying an active agent-permeable membrane;

e. a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer;

f. an adhesive overlay having a central portion overlying the backing layer and a peripheral portion that extends beyond the periphery of the peel seal disc; and

g. a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc.

Claim 17: A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of any of claims 3 to 5.

Claim 30: [A transdermal device comprising a means for adhering a drug reservoir to the application situs and the transdermal formulation of any of claims 3 to 5, and an effective amount of a drug permeation enhancer], wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

Claim 32: A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a free form hydroalcoholic gel and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

Claim 36: A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a liquid reservoir drug formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

2. OBVIOUSNESS

Claims 3-5, 14, 17-19 and 22-40 stand rejected under 35 U.S.C. § 103 as obvious in view of Cormier[1] and Ke.[2] The claims have been argued in six groups: claims 3-5, 28, 29, and 40 (group 1); claims 30 and 31 (group 2); claims 14, 18, 19, and 25-27 (group 3); claims 17 and 22-24 (group 4); claims 32-35 (group 5); and claims 36-39 (group 6). The claims in each group stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

With regard to claim 3, the Examiner relies on Cormier for disclosing "a transdermal formulation comprising an adhesive matrix reservoir" (Ans. 3). The Examiner finds that Cormier discloses that the "transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene" but "lacks a disclosure of lasofoxifene" (*id.* at 4).

The Examiner relies on Ke as disclosing a combination of "active agents in a transdermal ... including lasofoxifene" (*id.*, citing Ke at claim 1). The Examiner also relies on Ke as disclosing that droloxifene, raloxifene and tamoxifen can be used in the disclosed combination therapy in place of lasofoxifene (*id.*).

The Examiner concludes that it "would have been obvious to include the lasofoxifene" of Ke into the device of Cormier "since they comprise similar components, and are within the same field of endeavor" (*id*). The Examiner further concludes that it "would have been obvious to make the simple substitution and combination with an expected result of a viable

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[1] Cormier et al., US 6,203,817 B1, Mar. 20, 2001
[2] Ke et al., US 6,323,232 B1, Nov. 27, 2001

transdermal device useful in treating various estrogen related disorders" (*id.* at 4-5).

We conclude that the Examiner has set forth a prima facie case that claim 3 would have been obvious to the ordinary artisan. Cormier discloses "compositions, devices, and methods for transdermal administration of non-zwitterionic drugs ... wherein the compositions and devices are provided with a salt of a non-zwitterionic drug" (Cormier, col. 5, ll. 20-25). Cormier discloses that the device "may be a passive transdermal device known in the art" (*id.* at col. 5, ll. 55-57). Cormier also discloses that examples of drugs to be administered include "antiestrogen such as tamoxifen; and antiosteoporotic agents such as raloxifen [sic]" (*id.* at col. 7, ll. 66-67). Cormier discloses that the matrix reservoir for the drug may be a pressure sensitive adhesive (*id.* at col. 9, l. 61).

Ke discloses "[p]harmaceutical combination compositions including certain estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists ... useful for the treatment of bone disorders including osteoporosis" (Ke, abstract); preferred estrogen agonists/antagonists include raloxifene and tamoxifen (*id.* at col. 3, l. 49). Ke also discloses a "pharmaceutical composition comprising synergistic effective amounts of lasofoxifene and PGE2 in a pharmaceutically acceptable carrier" (Ke, claim 1). Ke also discloses transdermal dosage forms (*id.* at col. 37, ll. 49-52).

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art to combine the teachings of Cormier and Ke and thereby arrive at the invention of claim 3. Ke teaches that lasofoxifene formulations may be administered transdermally and that lasofoxifene is an

estrogen agonist/antagonist comparable to raloxifene and tamoxifen. Cormier teaches that a matrix reservoir for transdermal administration of raloxifene and tamoxifen (among other things) may be a pressure sensitive adhesive. Thus, it would have been obvious to one of skill in the art to administer lasofoxifene, like raloxifene and tamoxifen, transdermally via an adhesive drug matrix reservoir.

Appellants argue that "one of ordinary skill in the art would not be motivated to combine the publications" because the lasofoxifene, raloxifene, and tamoxifen "would be expected to have dramatically different chemical properties requiring unique formulations" and that

> the differing chemical structures and properties of tamoxifen and raloxifene as compared to lasofoxifene actually *teach away* from combining lasofoxifene with the transdermal delivery system discussed in Cormier *et al.* because the compounds are so structurally different that one of ordinary skill would not reasonably expect them to behave in the same manner ... when formulated into a drug matrix.

(App. Br. 15-16).

We are not persuaded by this argument. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 1740.

Although the raloxifene and tamoxifen disclosed in Cormier are structurally different than Ke's lasofoxifene, Ke expressly suggests transdermal administration of a composition that can contain lasofoxifene

(Ke, claim 1), raloxifene or tamoxifen (*id.* at col. 3, l. 49). Cormier describes an adhesive drug matrix reservoir for the transdermal administration of compounds including raloxifene and tamoxifen (Cormier, col. 7, ll. 66-67). The evidence therefore shows that it would be well within the skill of one in the art to formulate the lasofoxifene of Ke in Cormier's matrix for transdermal administration. The combination of the lasofoxifene of Ke with the adhesive drug matrix reservoir of Cormier appears to be nothing more than the combination of old elements for their expected function to yield predictable results.

With regard to claim 17, Appellants argue that "the Examiner has failed to show how the cited publications disclose or suggest the methods of treatment and prevention" (App. Br. 17).

We are not persuaded by this argument. As set forth above, the combination of Ke and Cormier would have made obvious the transdermal formulation of claim 3 that contains lasofoxifene. Ke discloses that the disclosed compositions are useful for treating osteoporosis (Ke, col. 3, ll. 37-42). Ke also discloses that "[w]omen experience a sharp acceleration of bone loss immediately following menopause" and that "[e]strogen is the agent of choice in preventing osteoporosis or post menopausal bone loss in women" (Ke, col. 1, ll. 31-37). Thus, one of skill would understand that osteoporosis is a disease associated with estrogen deficiency or disregulation and that the suggested lasofoxifene transdermal formulation would be useful in treating osteporosis. Ke and Cormier therefore would have suggested the method of claim 17 to a person of ordinary skill in the art.

With regard to claim 30, Appellants argue that "the Examiner has not cited any publication describing an effective amount of a cell-envelope disordering compound ... nor how a method using such a compound would be obvious" (App. Br. 19, emphasis omitted).

We are not persuaded by this argument. The Specification provides several examples of cell-envelope disruptors; they include isopropyl myristate, methyl laurate, etc. (Spec. 7, ll. 16-19). Originally filed claim 10 specifies that cell-envelope disordering compounds also include "a lower alkanol." Thus, we interpret the term "cell envelope disordering compound" to include at least lower alkanols and the compounds listed in the Specification as cell-envelope disruptors.

Cormier discloses, as recognized by the Examiner (Ans. 8), that propylene glycol is a component of its transdermal formulations (e.g. Cormier, Examples 1, 2, and 4). Thus, the combination of Cormier and Ke would have suggested to one of skill in the art the formulation of lasofoxifene with propylene glycol. Another name for propylene glycol is propane-1,2-diol. When we give the claim term "cell-envelope disordering compound" its broadest reasonable interpretation in light of the Specification, we conclude that "lower alkanol" reasonably appears to encompass propane-1,2-diol; i.e., propylene glycol. Therefore, we agree with the Examiner that the cited references would have suggested lasofoxifene formulated with a cell envelope disordering compound.

With regard to claim 14, Appellants argue that "the Examiner has not cited any publication describing claim elements such as the peel seal disc underlying the active agent permeable membrane, the heat seal about the

periphery of the peel seal disc and the removable release liner" (App. Br. 21, emphasis omitted).

We agree with Appellants that the Examiner has not adequately explained why a device meeting all the limitations of claim 14 would have been obvious to a person of ordinary skill in the art based on Cormier and Ke. The Examiner relies on element 24 of Cormier's device as "act[ing] as a protective peel seal disk in the transdermal device" (Ans. 7). Cormier, however, describes element 24 as a "strippable release liner" (Cormier, col. 9, ll. 56-58). Claim 14 requires both a release liner (claim 14, part g) and a peel seal disc (claim 14, part d). The release liner underlies the peel seal disc; thus, the two claim elements cannot be met by a single element in the prior art device. The rejection of claims 14, 18, 19, and 25-27 is reversed.

With regard to claim 32, Appellants argue that the "Examiner has not cited any publication describing a transdermal formulation comprising a free form hydroalcoholic gel" (App. Br. 23, emphasis omitted).

We are not persuaded by this argument. The Specification does not define "hydroalcoholic gel" but describes "**Free Form Hydroalcoholic Gel Preparation**" as being prepared by mixing ethyl alcohol, water, glycerin, enhancer, drug, and gelling agent (Spec. 12, ll. 4-8). Thus, we interpret the term hydroalcoholic gel to mean a gel containing alcohol and water.

Cormier discloses transdermal formulations that are aqueous gels that contain ethanol (e.g. Cormier, Examples 1, 2, and 4). Cormier further discloses that the drug reservoir can be formed of a rubbery polymer or an aqueous gel (*id.* at col. 9, ll. 28-31). Thus, the combination of Cormier and

Ke would have suggested to one of skill in the art lasofoxifene formulated in a free form hydroalcoholic gel.

With regard to claim 36, Appellants argue that "the Examiner has not cited any publication describing a transdermal delivery device comprising liquid reservoir drug formulation" (App. Br. 24-25, emphasis omitted).

We are not persuaded by this argument. The Specification provides that a "matrix patch is distinguished from a 'liquid reservoir patch,' wherein an active permeant or drug is dissolved in a gelled liquid" (Spec. 6, ll. 11-13). Thus, we interpret the term "liquid reservoir" to encompass a reservoir in gel form. As discussed above, Cormier discloses transdermal formulations that are gelled liquids. Thus, the combination of Cormier and Ke would have suggested to one of skill in the art lasofoxifene formulated in a liquid reservoir form (i.e., a gelled liquid form).

NEW GROUND OF REJECTION

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection: claims 14, 18, 19, and 25-27 are rejected under 35 U.S.C. § 103 as obvious in view of Ebert,[3] Cormier, and Ke. Ebert teaches the device defined by claim 14 (Ebert, Fig. 1 and col. 2, l. 60 to col. 3, l. 10) but does not expressly suggest using the device to administer lasofoxifene. Cormier and Ke suggest administering lasofoxifene transdermally for the reasons discussed at length above. It would have been obvious to a person of ordinary skill in the art to combine Ebert's device with the transdermal administration of lasofoxifene suggested by Cormier and Ke because Ebert states that the disclosed device is useful for administering a variety of

[3] Ebert et al., U.S. Patent 5,662,925, issued Sept. 2, 1997.

agents, including estradiol (Ebert, col. 4, l. 20). Combining the cited references thus amounts to "the predictable use of prior art elements according to their established functions." *KSR*, 127 S Ct. at 1740. The additional limitations of claims 18, 19, and 25-27 would have been obvious for the reasons discussed above with respect to claims 17 and 30.

SUMMARY

We affirm the rejection of claims 3-5, 17, 22-24, and 28-40 under 35 U.S.C. § 103. We reverse the rejection of claims 14, 18, 19, and 25-27 as obvious in view of Cormier and Ke. We enter a new ground of rejection of claims 14, 18, 19 and 25-27.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review.

37 CFR § 41.50(b) also provides that the Appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner . . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record . . . .

AFFIRMED-IN-PART, 37 C.F.R. § 41.50(b)

LP

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